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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,147	10/05/2000	Tomoki Todo	066683/018SB	7711

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/679,147	TODO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-9,12-16,19-30,32,33,35-37,48,49 and 52-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-9,12-16,19-30,32,33,35-37,48,49 and 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 12/4/03 has been entered. Claims 1-2, 7-9, 12-16, 19-30, 32-33, 35-37, 48-49, and 52-57 are pending and currently under examination in the instant application. An action on the merits follows.

Applicant's response is a copy of the supplemental response originally filed by applicant's on 6/19/03. The original copies of these papers were not matched with the application, which as of 9/9/03 was still a paper case. As such, the office action mailed on 9/9/03 did not take into consideration applicant's remarks presented in the supplemental response and was solely directed to the amendments and arguments presented in the amendment and response received on 6/16/03 which was matched with the paper case. The applicant's representative called the examiner after receiving the office action on 9/9/03 and brought to the examiner's attention the fact a supplemental amendment was filed on 6/19/03. At this point, the examiner discovered that the papers filed on 6/19/03 had in fact been received by the office and scanned, but had not been entered into PALM or matched with the case. The examiner indicated that the arguments presented in the supplemental response filed on 6/19/03 would be considered and addressed in the next office action, which would be made non-final as a result of the error by the office. Therefore, it is noted for the record that this office action is non-final.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

Claims 1-2, 7-9, 12-16, 19-30, 32-33, 35-37, 48-49, 52-54, and 57 stand rejected under 35 U.S.C. 112, first paragraph, for scope of enablement. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

Applicant's arguments presented in the instant response have not overcome the following issues for reasons of record: 1) lack of enablement for making and using soluble co-stimulatory molecules other than B7-1-Ig or B7-2-Ig; 2) lack of enablement for the use of vectors other than HSV vectors; and 3) lack of enablement for vectors capable of "targeting" particular types of cells.

The arguments presented in the instant response are solely directed to issue 3) as identified above. Regarding issue 3), which concerns the targeting of the vector to tumor cells, the applicant previously amended the claims to delete language regarding targeting the vector to tumor. However, the applicant also amended the claims to delete the limitation that the composition would be administered by localized delivery. With the exception of claims 7-9, and 25, which recite that the nucleotide sequence or composition is administered directly to the tumor, the method claims, claims 1-2, 12-16, 19-22, 24, 26-30, 52-53, and 57, read on the use of any route of administration such that the factor is expressed by tumor cells or cells in the

immediate area of the tumor. The previous office actions provided substantial evidence regarding the lack of predictability in targeting vector delivery and gene expression to particular cell types *in vivo*, citing Deonarian and Miller. In response, the applicant argues that herpes simplex virus can effectively target a tumor when the virus is not administered directly to the tumor and provides several publications in support of their arguments. Exhibits 1, 2, and 4 were published before the effective filing date of the instant application which is October 5, 1999, and as such represent the state of the art at the time of filing. Exhibits 3, and 5-8 were all published after the effective filing date. However, the take-home message from all of these references is that HSV virus needs to be delivered near the tumor in order for effective targeting to tumor cells. Kooby et al. teaches direct injection and local injection of G207 to colon carcinomas. Oyama et al. teaches local delivery of G207 by intravesicle administration to the bladder to target a bladder tumor. Carew et al. teaches local delivery of G207 to tumor in the cheek pouch by injection of the virus into the external carotid artery which the authors indicate was shown to directly supply the cheek pouch in hamsters. Bennett et al. teaches local delivery of G207 to intraperitoneal tumors by intraperitoneal injection of the virus. Cozzi et al. teaches local delivery of G207 to the bladder by intravesicle injection to target tumor present in the bladder. Ebright et al. teaches local delivery of HSV into lungs with tumors by intrapleural injection. Thus, all of these references provide strong support for local delivery of HSV in order to target tumors. The only other non-local route of delivery contemplated by several of the publications is intravenous delivery. While Walker et al. and Carew et al. show that intravenous delivery of G207 into immunocompromised athymic mice results in some anti-tumor effects, these experiments cannot be correlated to the situation in immunocompetent mammals where anti-viral immune responses

can substantially effect virus half-life and efficacy. Furthermore, even in athymic mammals, intravenous administration of HSV in not always effective. This is demonstrated by Ebright et al. who show that intravenous administration of G207 in nude rats is ineffective in treating tumors located in the lungs. Thus, at the time of filing, e.g. 1999, it is clear that the state of the art only recognized direct or local administration of HSV for tumor treatment, and that intravenous delivery was only contemplated in immunocompromised hosts. Note that the claims are not so limited. Finally, only Delman et al., published after the effective filing date of the instant application demonstrates any effect on a tumor in immunocompetant mammals by intravenous administration of HSV. However, Delman et al. concludes from their results that HSV-based oncolytic therapy requires the delivery of the HSV in "reasonable proximity" to the tumor. Thus, even after the effective filing date, the skilled artisan considered that tumor targeting with HSV required local or regional delivery of the HSV. Therefore, applicant's evidence does not support their argument that the skilled artisan would have predicted success in using routes of HSV delivery other than administration at or near a tumor.

The instant response does not provide any new arguments regarding the other two issues concerning enablement identified above. For clarity of prosecution, the grounds of rejection pertaining to issues 1) and 2) are reiterated below.

Regarding issue 1), the applicant previously amended claims 55-56 to recite wherein the soluble costimulatory molecule is B7-1-Ig and therefore these claims have been withdrawn from the instant rejection of record. However, claims 1-2, 7-9, 12-16, 19-30, 32-33, 35-37, 48-49, 52-54, and 57 have not been so amended and continue to read broadly on any soluble costimulatory molecule in the B7 family or any soluble B7-1 molecule. The previous office action stated that

the evidence of record, i.e. the specification and publications by Kato et al., Kanner et al., Noelle et al., and Hurtado et al., while demonstrating that it was within the skill of the artisan to make a soluble co-stimulatory molecule comprising the extracellular domain of a co-stimulatory molecule and IgG, does not provide enablement for making soluble co-stimulatory molecules that do not contain IgG. The applicant's have not provided any arguments regarding this issue. Therefore, the rejection of record regarding this issue is maintained over claims 1-2, 7-9, 12-16, 19-30, 32-33, 35-37, 48-49, 52-54, and 57 .

Regarding issue 2), the applicant's previous amendments overcame this grounds of rejection for claims 2, 23, 32-33, 35-37, 48-49, 54, and 57 by amending the claims to recite an HSV vector encoding the soluble B7 costimulatory factor. However, claims 1, 7-9, 12-16, 19-22, 24-30, and 52-53 have not been so limited. Claim 1, from which claims 7-9, 12-16, 19-22, and 52 depend recites a composition comprising an expressible nucleotide sequence for a soluble B7 costimulatory sequence and a herpes simplex virus vector. As such, the soluble B7 may be contained in any type of expression construct not limited a herpes simplex virus vector. Claim 24, from which claims 25-30, and 53 depend, continues to recite that the composition comprises an expressible nucleotide sequence for a soluble B7 costimulatory factor. These claims do not contain any recitation of a herpes simplex virus vector. Again, in these claims, the soluble B7 may be contained in any type of expression construct. The previous office actions have addressed in detail the unpredictability of using any and all vectors in applicant's instant invention, and the fact that the specification also does not provide an enabling disclosure for using any vector/promoter combination to express therapeutic amounts of B7-1-Ig *in vivo*, citing Verma et al., Marshall et al., Orkin et al, and Fry et al. and Roth et al. The applicant has not

provided any arguments addressing this issue. Therefore, the rejection of record regarding this issue is maintained over claims 1, 7-9, 12-16, 19-22, 24-30, and 52-53.

For the record, the following subject matter is considered to be enabled by the specification and evidence of record: 1) pharmaceutical compositions comprising a herpes simplex virus vector encoding a soluble costimulatory factor selected from the group consisting of B7-1-Ig and B7-2-Ig; and 2) methods of activating or enhancing a T-cell response in a patient with a tumor comprising administering a pharmaceutical composition comprising a herpes simplex virus vector encoding a soluble costimulatory factor selected from the group consisting of B7-1-Ig and B7-2-Ig directly into said tumor or a local area of said tumor, such that said factor is expressed by tumor cells or cells in the immediate area of the tumor, and said T-cell response thereby is activated or enhanced against said tumor.

The rejection of claim 57 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained. Claim 57 depends on claim 24. There is no antecedent basis in claim 24 for "said herpes simplex vector" as recited in claim 57. The applicant has not amended the claims or presented any arguments in response to this rejection. Therefore, the rejection of record stands.

Duplicate Claims/Claim Objections

Applicant is advised that should claims 23 and 55 be found allowable, claims 32 and 56 respectively will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are dupplicates or else are so close in content that they both

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claims. See MPEP 706.03(k). In the instant case, claims 23 and 32 are so close in content that they cover the same thing despite a slight difference in wording. Claims 55 and 56 depend on claims 23 and 32 respectively and recite identical limitations.

Please note that claims 55 and 56 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. However, as noted above, should claims 55 and 56 be amended such that they are allowable, claim 56 will be objected to as a duplicate claim.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER